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Fe-Catalyzed Hydroalkylation of Olefins with *para*-Quinone Methides

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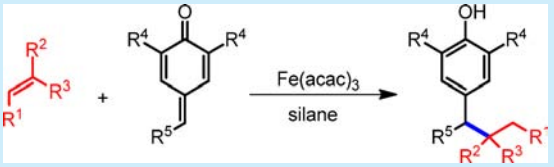
Supporting Information

ABSTRACT: A novel Fe-catalyzed hydroalkylation of olefins with *para*-quinone methides (*p*-QMs) for accessing phenols has been developed. In this protocol, various olefins could convert to alkyl radicals and undergo addition to *para*-quinone methides toward C−C bond formation and aromatization. The reaction conditions are mild and the substrate scopes are broad.



In recent years, the transition-metal-catalyzed radical olefin hydrofunctionalization has been shown as an effective and distinct approach for C−C and C−N bond formation.[1] Halpern first revealed the evidence of radical mechanism for Mn-catalyzed hydrogenation of α-methylstyrene,[2] and Mukaiyama developed a Fe-catalyzed olefin hydroamination for accessing amines.[3] Magnus reported a Mn-catalyzed hydroxylation of α,β-unsaturated ketones.[4] Carreira developed various transition-metal-catalyzed heterofunctionalization of olefins.[5] Recently, Shenvi developed Mn- and Co-catalyzed olefin hydrogenations that deliver thermodynamically preferred stereoisomers via radical mechanism.[6] Boger extended the Fe-catalyzed olefin hydrofluorination and hydroamination method using selectfluor and NaN_3 as fluorination and amination sources, respectively.[7] More recently, Baran invented Fe-catalyzed practical reductive olefin coupling, olefin hydroamination and hydromethylation to afford valuable hindered amines and natural product analogues.[8] Notably, these olefin hydrofunctionalization strategies have been applied in total synthesis of natural products. For example, Maimone realized a four-step synthesis of the antimalarial cardamom peroxide with a key step of Mn-catalyzed olefin hydropreoxidation.[9] More recently, Pronin reported a concise approach to paxilline indole diterpenes, and the key step relies on Fe-catalyzed hydrogen atom transfer (HAT) to enable the sequential polycyclization for the construction of tricyclic core.[10] Therefore, the development of olefin hydrofunctionalization toward C−C and C−N formation is important and interesting.

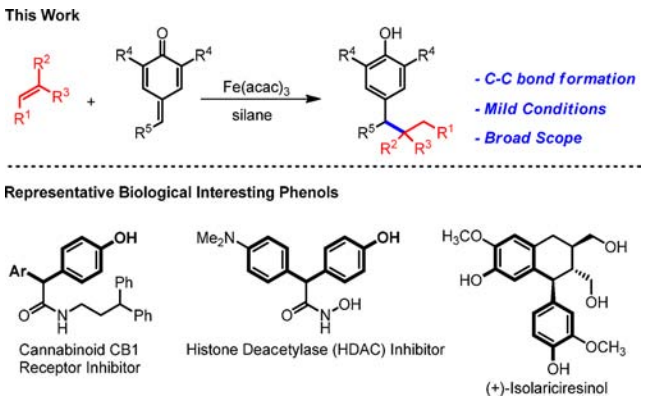
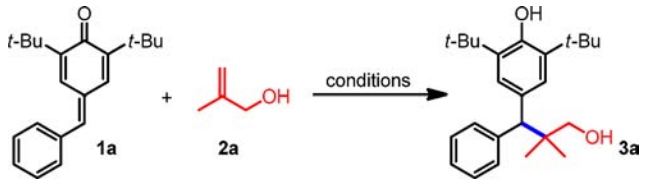


Figure 1. Fe-catalyzed olefin hydroalkylation with *p*-QMs for phenol synthesis.

Table 1. Optimization of the Reaction Conditions[a,b]



entry	Fe(III) salt	reductant	solvent	t (°C)	yield (%)[b]
1	$Fe(acac)_3$	$PhSiH_3$	EtOH	60	49
2	$Fe(acac)_3$	$PhSiH_3$	DCM	60	trace
3	$Fe(acac)_3$	$PhSiH_3$	DMF	60	trace
4[c]	$Fe(acac)_3$	$PhSiH_3$	THF	60	87
5[c]	$Fe_2(ox)_3{\cdot}6H_2O$	$PhSiH_3$	THF	60	trace
6[c]	$Fe(acac)_3$	Et_3SiH	THF	60	trace
7[c]	$Fe(acac)_3$	$PhSiH_3$	THF	25	21

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Fe(III) salt (30 mol %), reductant (0.2 mmol), in 1 mL of solvent under argon for 2 h. [b]Isolated yields are given. [c]EtOH (0.4 mmol) was added as additive.

para-Quinone methides (*p*-QMs), which are structurally characterized by the unique assembly of carbonyl and olefinic moieties, are known as a versatile building block and widely used in the synthesis of natural products and bioactive molecules.[11] Evans reported an intramolecular electrophilic cyclization of masked *p*-QMs and applied to total synthesis of (±)-cherylline.[12] Angle reported a *p*-QMs initiated cyclization reaction and revealed that *p*-QMs could serve as versatile Michael acceptors.[13] Recently, Fan and co-workers developed an asymmetric catalytic 1,6-conjugate addition/aromatization of *p*-QMs for enantioselective introduction of functionalized diarylmethine stereogenic centers.[14] Jørgensen also reported an organocatalytic asymmetric

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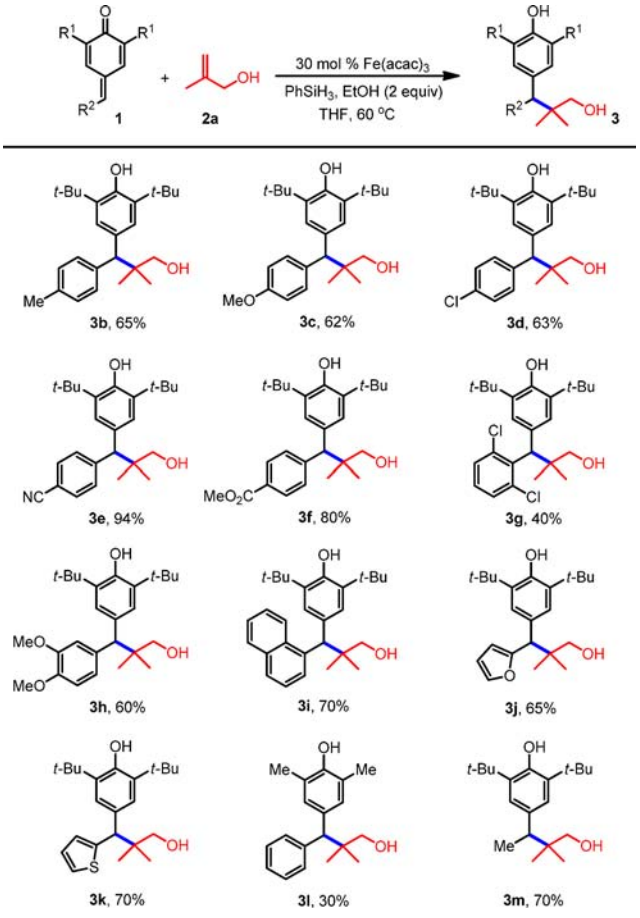
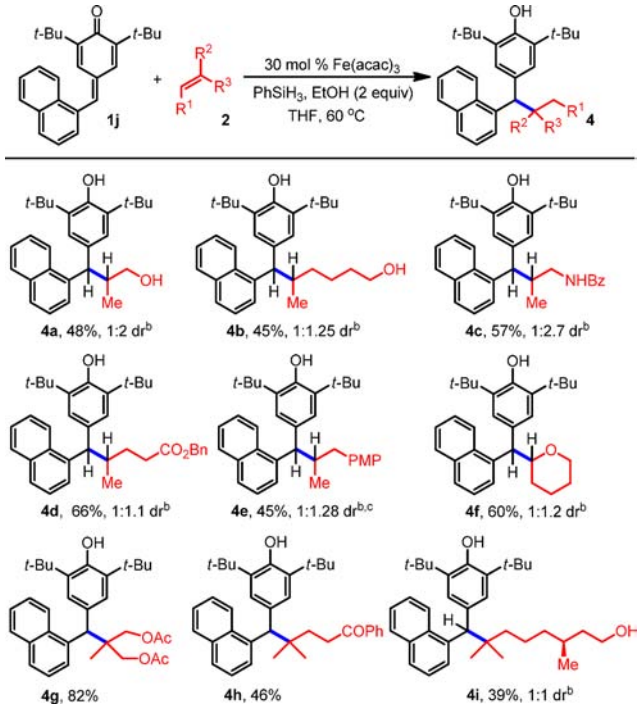
Scheme 1. Scope of the *p*-QMs[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $Fe(acac)_3$ (30 mol %), $PhSiH_3$ (0.2 mmol), EtOH (0.4 mmol), in THF (1 mL) at 60 °C for 1 h, argon. [b]Isolated yields are shown.

Scheme 2. Scope of the Olefins[a]



[a]Standard condition, isolated yields are shown. [b]dr was identified by HNMR. [c]PMP = *para*-methoxyphenyl.

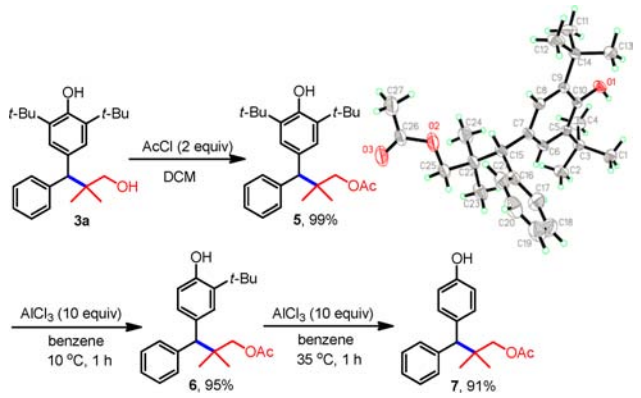


Figure 2. Transformation of the product.

α-alkylation of aldehydes by 1,6-conjugated addition of enamines to *p*-QMs.[15] Meanwhile, Liao, Tortosa, and Li reported the asymmetric 1,6-boration, and 1,6-thiolation of *p*-QMs, respectively.[16] More recently, Deng, Enders, and Fan independently developed the asymmetric addition of *p*-QMs with glycine Schiff base and oxindoles.[17] However, Anand reported that the *N*-heterocyclic carbene (NHC)-catalyzed 1,6-conjugate addition of *p*-QMs with aldehydes for access to α,α'-diarylated ketones.[18] Surprisingly, few radical type reactions of *p*-QMs have been documented, and therefore, this area remains to be explored.

Pursing our interests in Fe-catalyzed olefin hydrofunctionalization and heterocycles synthesis,[19] we proposed that Fe-catalyzed HAT of olefins could generate alkyl radicals, which would probably take addition to *p*-QMs toward hydroalkylation. Herein, we wish to report a Fe-catalyzed olefin hydroalkylation with *p*-QMs for accessing phenols (Figure 1).

We commenced our study by investigating *p*-QMs **1a** and 2-methylallyl alcohol **2a** (Table 1). Initially we carried out the reaction using $Fe(acac)_3$ as the catalyst and $PhSiH_3$ as the reductant in ethanol at 60 °C. Gratifyingly, a phenol product **3a** was observed and isolated in 49% yield (entry 1). This encouraged us to further optimize the reaction conditions. The survey of solvent showed that DCM and DMF were inferior to give trace product (entries 2−3). To our surprise, when the reaction was conducted in THF with 2 equiv amount of EtOH as additive, we were pleased to find that the yield of **3a** could be dramatically improved to 87% (entry 4). The next variation of the catalyst to $Fe_2(ox)_3{\cdot}6H_2O$ only afforded trace product (entry 5). When the reductant was changed to Et_3SiH, the reactivity was completely shut down (entry 6). Meanwhile, decreasing the temperature to 25 °C would also lead to a significantly lower yield (entry 7).

With the optimized condition in hand, we set out to explore the substrate scope of this transformation (Scheme 1). Various *p*-QMs served as viable acceptor in this hydroalkylation process. For example, the 4-substituted *p*-QMs, regardless of the electron-donating or electron-withdrawing substitution, could proceed smoothly in this process to deliver corresponding phenols in good to excellent yields (**3b**−**3f**), with the valuable functional group like methyl, methoxy, chloro, cyano, and ester. The electron-withdrawing group substituted *p*-QMs could afford higher yield than those electron-donating substituted *p*-QMs, probably because of their electron-withdrawing nature to enable a higher reactivity. Moreover, the polysubstituted *p*-QMs were

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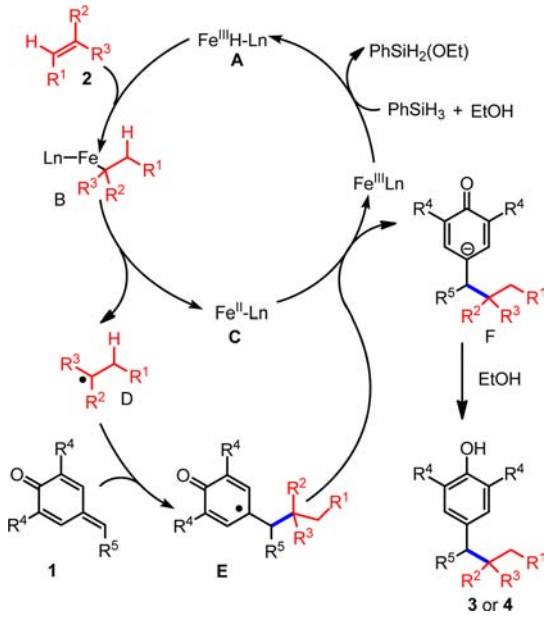

Figure 3. Proposed mechanism.

also well applicable in this protocol to deliver the phenols in moderate to good yields (**3g**-**3h**). Interestingly, the 1-naphthanyl and heterocyclic substituted *p*-QMs, like furan and thiophene, were also amenable to this protocol to generate the corresponding phenols in good yields (**3i**−**3k**). When 2,5-dimethyl *p*-QMs **1m** was used, the phenol product could also be formed, albeit in a slightly lower yield (**3l**, 30%). Moreover, the alkyl substituted *p*-QMs were also applicable in this process to furnish the product in good yield (**3m**, 70%). Considering the wealth of phenols in natural products and medicinal chemistry, this method provides a simple and rapid access to structurally differential phenols, with readily available starting materials and broad scope.[20]

Next, the scope of olefins was tested to react with *p*-QMs **1i** (Scheme 2). Gratifyingly, various olefins were well applicable in this hydroalkylation process. The terminal olefins with those substituents, such as hydroxy, amide, ester, and PMP, were well tolerated to furnish the products in moderate to good yields. The coupling constant of the two hydrogen atoms was about 10.8 Hz (Scheme 2, **4a**−**4e**). The value of diastereo ratio depended on their functional groups, ranging from 1:1.1 to 1:2.7. The cyclic olefin such as dihydropyran was also applicable to afford the product **4f** with 1:1.2 dr value. The other disubstituted olefins with functional groups like ester, ketone, and hydroxy were also tested in this hydroalkylation process to afford the products in moderate to good yields (**4g** and **4h**). Additionally, when (*S*)-(−)-*β*-citronellol **2j** was subject to this protocol, this reaction could afford the product **4i** in moderate yield with 1:1 dr value. Therefore, this method represents a distinct approach toward phenols.

The synthetic applicability of this protocol was also demonstrated by the transformation of the compound **3a** (Figure 2). The acetylation of the alcohol hydroxyl group of **3a** to **5** was carried out at the beginning, and the structure of **5** was confirmed by X-ray analysis.[21] The next stepwise $AlCl_3$-mediated de-*tert*-butylation of **5** was conducted. We found the *tert*-butyl group could be successively removed by a temperature-dependent reaction condition, and the de-*tert*-butylation products **6** and **7** could be afforded in good yields.

Based on these results and relevant literature, a plausible mechanism for this olefin hydroalkylation is proposed in Figure 3. At the beginning, the Fe(III)-catalyst is converted to Fe hydride species **A** treated with phenylsilane and ethanol.[6−8,19a,b] Then Fe species **A** undergo addition to olefin **2** to produce **B**. This addition is regioselective and the Fe atom was placed on the more substituted carbon atom. The following dissociation of **B** generates Fe(II) species **C** and alkyl radical **D**, which is trapped by *p*-QMs **1** to form intermediate **E**. The single-electron transfer between **E** and **C** delivers **F**, which is protonated and rapidly isomerizes to furnish the phenol products to realize hydroalkylation and regenerate Fe(III) to enable the catalytic cycle.

In summary, a Fe-catalyzed olefin hydroalkylation with *para*-quinone methides for accessing phenols has been reported. This protocol is not only featured with mild conditions and broad scope, but also reveals a radical-type addition reaction of *p*-QMs, which would offer a new insight for *p*-QM transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01173.

Full experimental procedures, characterization data, and NMR spectra data (PDF)

Crystallographic data for **5** (CIF)

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Notes

The authors declare no competing financial interest.

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